Docket No.: P0786.70000US05
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John B. Sullivan et al.
Serial No.:	08/405,454
Confirmation No.:	6004
Filed:	March 15, 1995
For:	ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS
Examiner:	R. B. Schwadron
Art Unit:	1644

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Dated: _____ Signature: _____ ( )

DECLARATION OF RICHARD C. DART, M.D., PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Richard C. Dart, hereby declare as follows:

1. I am currently the Director of the Rocky Mountain Poison and Drug Center, a position I have held since 1992. I am also a Professor of Surgery (Emergency Medicine), Pharmacy, and Medicine at the University of Colorado Health Sciences Center.

2. From 1986 to 1991, I was a doctoral student at the University of Arizona College of Pharmacy, receiving a Ph.D. in Pharmacology/Toxicology in 1991.

3. From 1985 to 1987, I was a Clinical Toxicology Fellow at the University of Arizona Health Sciences Center. My fellowship director was Dr. John B. Sullivan, and I worked there with Dr. Findlay E. Russell, who are the two inventors of this Application

4. From 1983 to 1985, I was a Resident in Emergency Medicine at the University of Arizona Health Sciences Center, Tucson, AZ.

5. From 1982 to 1983, I was a Resident in Internal Medicine at the Albany Medical Center, Albany, NY.

6. From 1981 to 1982, I was an Intern in Internal Medicine at the Albany Medical Center, Albany, NY.

7. From 1977-1981, I was a medical student at Wayne State University School of Medicine, Detroit, MI, receiving an MD in 1981.

8. I received a BS. in Biology from Albion College, Albion, MI in 1977.

9. As shown in my attached C.V. [Ex. 1], I have published over 175 articles, chapters, editorials, and letters. I am the editor of *The Five Minute Toxicology Consult* (First Ed.) and *Medical Toxicology* (Third Ed.), which has been called the industry's reference and text book.

10. I was the 2004 recipient of the American College of Medical Toxicology Matthew J. Ellenhorn Award for Excellence in Medical Toxicology and am currently President-Elect of the American Association of Poison Control Centers.

11. Much of my clinical, consulting, and research experience relates to the treatment of snake bites with antivenoms. I have served as Principal Investigator for several clinical trials on different antidotes, I have consulted for several different biopharma companies (including the assignee, Protherics, Inc.) regarding antivenom use and development, and I continue to do so. I was the Principal Investigator for the clinical trial of CroFab that ultimately resulted in it being approved by the FDA. For this research, I was awarded the Food And Drug Administration's Special Citation in 2001.

12. The antivenom field is relatively small, and I consider myself to be an expert on the topic. I also consider myself to have been one of ordinary skill in the field as of October 9, 1984. At that time I was over 3 years into my career as an M.D., including one year as a Resident in Emergency Medicine at the University of Arizona Health Sciences Center, whose Emergency Room treats as many snake bite victims as any other Emergency Room in the United States. I was also preparing to start my Fellowship in Clinical Toxicology.

13. I have been retained as a testifying expert by Wolf Greenfield & Sacks, the law firm representing the assignee Protherics, Inc. in this matter. The Rocky Mountain Poison and Drug Center is being paid at the rate of $500 per hour for my time spent reviewing materials, consulting, and preparing this declaration. I have no financial interest in whether a patent issues from this application.

14. I have read the Decision on Appeal dated June 15, 2009. [Ex. 2.] I disagree with its conclusion that one of ordinary skill in the art would have been motivated to prepare an antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and a pharmaceutically acceptable carrier, with a reasonable expectation that the composition would neutralize the lethality of the venom of a snake of the Crotalus genus. [Ex. 2 at p. 16, second full paragraph; p. 16, last paragraph, through page 17, first full paragraph.]

15. I first note that the Decision bases its conclusion on the assertion that the Fab teachings of the Coulter et al. article [Ex. 3]would have led one of ordinary skill in the art to prepare Fab fragments of the affinity-purified antibodies of the Sullivan et al. article [Ex. 4] because the Fab fragments would be expected to have improved sensitivity in assays. [Ex. 2 at p. 16, first full paragraph.] I simply do not understand how this is relevant to the claimed invention, which I understand is:

> 40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as

> determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus

16. The Decision seems to ignore that this claim concerns an antivenom, not an antibody for an immunoassay. The Decision's posited immunoassay reagent would not be an "antivenom." It would not be a "pharmaceutical composition." It certainly would not be used by any clinician "for treating a snakebite victim." And no clinician would reasonably expect such an immunoassay reagent to "neutralize the lethality of the venom of a snake of the Crotalus genus."

17. It has been explained to me that the Decision refused to consider these elements of the claimed invention based on some legal analysis that is beyond my training and expertise. Regardless of any legal analysis, as one of at least ordinary skill in the art, I read claim 40 as requiring an *in vivo* purpose, use, property, and effect. Nothing in the combined teachings of the Sullivan et al. and Coulter et al. articles would have provided a reasonable expectation of "neutralizing the lethality of the venom of a snake of the Crotalus genus" with an "antivenom pharmaceutical composition" "for treating a snakebite victim" comprising Fab fragments that bound to the venom of a snake of the Crotalus genus.

18. The Decision misapprehends the Coulter et al. article. Coulter et al. showed that Fabs raised to a single toxin "isolated from the venom of the Australian brown snake, *Psuedonaja textilis*" [Ex. 3 at p. 199, last sentence] neutralized the lethality **of that single toxin**. [Ex. 3 at p. 201 third full paragraph.] Coulter et al. raised Fab fragments to textilotoxin (not whole venom) and tested those Fab fragments "for their ability to neutralize the lethal effects of textilotoxin [not whole venom] in mice." [Ex. 3 at p. 201 third full paragraph.]

19. The Decision repeatedly mischaracterizes the teachings of the Coulter et al. article, confusing the distinctions between an individual toxin of a snake venom and the entire snake venom. For example, the Decision states:

> Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 20, first paragraph (emphasis added).]
>
> Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at sentence bridging pp. 20-21 (emphasis added).]
>
> Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 21, last paragraph (emphasis added).]
>
> Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake **venom**. [Ex. 2 at p. 23, second full paragraph (emphasis added).]

20. None of these statements is true. The Coulter et al. article taught that Fab fragments were effective in neutralizing the lethality of a single venom toxin, **not** an entire snake venom. Appellants were the first to teach or suggest neutralizing the lethality of an entire snake venom with an antivenom comprising Fab fragments.

21. The combined teachings of the Coulter et al. article and the Sullivan et al. article would not have provided one of ordinary skill in the art with a reasonable expectation that Fabs could neutralize the lethality of:

> 1) *Psuedonaja textilis* venom as a whole by administering Fabs raised to just textilotoxin;
>
> 2) *Psuedonaja textilis* venom as a whole by administering Fabs raised to the entire venom; or
>
> 3) *Crotalus* venom as a whole by administering Fabs raised to *Crotalus* venom.

22. First, snake venoms are very complex mixtures of small and large molecules, including numerous toxins. They are so complex that most have not had all their components fully characterized, despite decades of research. Similarly, the properties of most venom components were not known in 1984, despite decades of research. However, many of the most toxic components of snake venoms have been identified and their properties generally classified. Thus, these toxins are sometimes referred to as, for example, neurotoxins, cardiotoxins, hemorrhagics, and fibrinolytics. These properties are not necessarily exclusive, and a particular toxin may have more

than one of these properties. Moreover, the individual toxins can interact synergistically with other toxins in a venom.

23. Nonetheless, most medically important venoms have been characterized in terms of the main toxic effect of their most clinically significant individual toxins, which can sometimes comprise a small percentage of a venom's total individual toxins. An antivenom must neutralize all of these clinically important toxins of a venom to neutralize the lethality of that venom. [Ex 5 at p. 83 ("An antivenom must be capable of neutralizing the injurious components of the venom."); 85 ("Thus, there may be a limited number of clinically important components that require neutralization."). Neutralizing the lethality of one toxin is not effective since other clinically important toxins could still cause lethality. [Ex. 6 at p. 319 col. 2 ("venoms are complex mixtures of proteins and other toxic factors could cause death.") ("Both the hemorrhagic and fibrinolytic activities need to be neutralized with antivenom.").]

24. *Psuedonaja textilis* was known in 1984 to have several clinically important toxins. Neutralization of the lethality of only one of those toxins, as shown in the Coulter et al. article, would not have been expected to result in neutralizing the lethality of the entire venom because the other lethal toxins would remain unneutralized. Indeed, the existing *Psuedonaja textilis* antivenom suffers from this very problem. It neutralizes the activity of textilotoxin, but it does not sufficiently neutralize the prothrombin activator, leading to coagulopathy and potentially fatal cerebral hemorrhage. [Ex. 7 at p. 80, first full paragraph. ("While CSL Ltd. antivenoms have saved many lives, persistent difficulties are being experienced with its inability to efficiently reverse the effects of the prothrombin activator. Unrelenting coagulopathy due to the slow reversal of prothrombin activator presents the added risk of cerebral hemorrhage to the victim.").] One of ordinary skill in the art would not have expected Coulter et al.'s Fab fragments to textilotoxin to have neutralized the lethality of the entire venom of *Psuedonaja textilis*. Neutralizing one weapon in the venom's arsenal of lethal toxins would not neutralize the activity of its other lethal toxins.

25. Second, one of ordinary skill in the art also would not have expected application of Coulter et al.'s Fab method to the entire venom to yield an antivenom that neutralized the lethality of

Psuedonaja textilis venom. Given the diversity in size, charge, and structure of snake venom toxins, Coulter et al.'s ability to obtain Fab fragments that neutralized the lethality of textilotixin would not have provided a reasonable expectation that one of ordinary skill in the art could have obtained Fab fragments that neutralized the lethality of the other clinically significant *Psuedonaja textilis* venom toxins.

26. An Fab fragment neutralizes the lethality of a venom toxin by binding to the toxin in such a way that it blocks the binding of the toxin to its target. The Fab can itself block the binding of the toxin via stearic hindrance (physically or by polarity), or the Fab can alter the structure of the toxin. In either case, the neutralization requires a specific binding between the Fab and the toxin. The Fab must have a specific 3-D structure and charge to bind the toxin so that it blocks its binding to the target. Otherwise, the Fab can bind to the toxin but have no effect on its activity. [Ex. 5 at p. 86 ("it is crucial to understand that binding of a venom component does not necessarily mean neutralization.").]

27. The only commonality between textilotoxin and other clinically significant *Psuedonaja textilis* venom toxins is that they are contained in *Psuedonaja textilis* venom. Like all snake venoms, *Psuedonaja textilis* venom is a complex mixture of very different molecules. Coulter et al.'s teaching that Fab could neutralize the lethality of textilotoxin would have provided no more guidance on the ability of Fabs to neutralize all the other clinically significant *Psuedonaja textilis* venom toxins than it provided on the ability of Fabs to neutralize any other combination of toxins. Indeed, I am not aware of Coulter et al. ever producing a *Psuedonaja textilis* antivenom comprising Fab fragments despite the great commercial importance of *Psuedonaja textilis* antivenom to their employer, CSL Laboratories, which produced several *Psuedonaja* antivenoms.

28. Third, even if Coulter et al. did produce an antivenom that neutralized the lethality of Psuedonaja textilis venom, one of ordinary skill in the art would not have had a reasonable expectation of success in extrapolating results with an antivenom to *Psuedonaja textilis* venom to an antivenom to Crotalus venom. The snakes are in two different genera—Psuedonaja and Crotalus. Indeed they are in two different families—Elapidae and Crotalidae. There are significant

differences between the venoms of those two families. The venom of elapids, while a complex mixture of chemicals, is relatively simple for snake venom. The venom of Crotalids, however, is extremely complex. Indeed, while Psuedonaja venoms can have 3-4 lethal toxins, Crotalus venoms have at least 6 lethal toxins. One of ordinary skill in the art would not have extrapolated antivenom results involving a single toxin of a relatively simple Psuedonaja venom to predict with any reasonable expectation of success what would happen with an antivenom to a much more complex Crotalus venom.

29. Immune reactions to Wyeth's Antivenin (Crotalidae) Polyvalent (ACP) had long been known to be a problem. The problem was so great that some clinicians refused to give ACP, and others felt stuck between the rock of not treating a snake bite victim with an antivenom and the hard place of treating a snake bite victim with an antivenom that might be worse for the victim than the venom being treated. The immune reactions were mainly attributed to 1) extraneous protein in the antivenom and 2) the presence of the Fc portion of the IgG molecules. The Sullivan et al. article addressed the first cause of those reactions by affinity purifying the IgG molecules that actually bound four target *Crotalus* venoms. [Ex. 4.] Before Applicants' invention, nobody had addressed the second aspect of this long-felt need for a safer antivenom, despite the major concern clinicians had regarding allergic reactions to ACP. I believe this is why the FDA granted CroFab orphan drug status.

30. Fab fragments had long been known to have potential application as an antidote, dating back at least to the use of Fabs to treat digoxin overdose in 1971. [Ex. 8 at p. 385, first paragraph.] And many antivenoms that eliminated the Fc fragment had been made and used. Those antivenoms, however, comprised $F(ab)_2$ fragments, not Fab fragments. $F(ab)_2$ fragments differ from Fab fragments by being split from the Fc portion below the hinge rather than above the hinge. The result is that $F(ab)_2$ fragments comprise two antigen binding sites, still joined at the hinge, while Fab fragments split into two separate binding sites. Despite the relatively widespread use of antivenoms comprising $F(ab)_2$ fragments, particularly in Australia, nobody prepared an antivenom comprising Fab fragments before the Applicants.

31. I believe nobody progressed to the smaller Fab fragments for two reasons. First, the $F(ab)_2$ fragment antivenoms were not as safe as had been anticipated, still resulting in allergic reaction in 30-84% of cases. [Ex. 5 at p. 90, second full paragraph.] Second, the bivalency of $F(ab)_2$ fragments allows them to bind and cross-link two toxins, often resulting in a large $F(ab)_2$-toxin complex being precipitated out of solution; monovalent Fab fragments cannot do that. The less than expected increase in safety of $F(ab)_2$ fragment antivenoms, combined with this potential for lower effectiveness of Fab fragment antivenoms, prevented those skilled in the art from proceeding to Fab fragment antivenoms.

32. Despite those concerns, the Applicants prepared a Fab fragment antivenom and tested its ability to neutralize the lethality of Crotalus venom. Unexpectedly, they found that the Fab fragment antivenom not only neutralized the lethality of Crotalus venom, but it did so both better than ACP and better than antivenom purified according to the Sullivan et al. article. Table 1 shows that the Fab fragment antivenom protected 6 of 9 mice from death, while ACP protected only 3 of 9. [Ex. 9 at p. 19.] Table 2 shows that the Fab fragment antivenom protected 2 of 4 mice from death, while ACP protected only 1 of 4. [Ex. 9 at p. 20.] Table 3 shows that the Fab fragment antivenom protected 4 of 4 mice from death, as did the antivenom prepared according to the Sullivan et al. article, while ACP protected only 1 of 4. [Ex. 9 at p. 20.] Table 4 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Ex. 9 at pp. 20-21.] Table 5 shows that the Fab fragment antivenom protected 5 of 5 mice from death while the antivenom prepared according to the Sullivan et al. article protected 3 of 5, and ACP protected 0 of 5. [Ex. 9 at p. 21.] Finally, Table 6 shows that the Fab fragment antivenom significantly delayed the time of death in mice given a dose that is lethal in 99% of subjects, compared to both the antivenom prepared according to the Sullivan et al. article, and ACP. [Ex. 9 at p. 22.]

33. Even if one of ordinary skill in the art were to read the Coulter et al. article as the Decision did—ignoring the very real and clinically important distinction between neutralizing a toxin of a venom and neutralizing the entire venom—these results are unexpected based on the Coulter et al.

article. The Coulter et al. article reported that Fab had the equivalent neutralization ability as its corresponding IgG **on a weight basis**. [Ex. 3 at p. 202, third paragraph.] IgG has a mass of approximately 150 kDa, while Fab has a mass of approximately 50 kDa. Thus, 3 times as many Fab fragments need to be given to have the same neutralizing ability as IgG according to the Coulter et al. article. Indeed, the Coulter et al. article concludes that "Fab fragments can be obtained from rabbit IgG **with losses of 20-30% of initial IgG antibody activity**." [Ex. 3 at p. 202, last paragraph (emphasis added).] Applicants' results surprisingly do not show such a loss in neutralizing ability for an Fab fragment antivenom. Instead, they show an increase in neutralizing ability for an Fab fragment antivenom.

34. This unexpected increase in effectiveness, combined with the increased safety, greatly interested clinicians in the field. CroFab, the commercial embodiment of the claimed invention, was first scientifically reported in the Consroe et al. article in 1995. [Ex. 10.] That article reported no adverse reactions in mice treated with CroFab. [Ex. 10 at p. 509, col. 1.] In line with the surprising results reported in the Application, it also reported that CroFab was on average 5.2 times more potent than ACP. [Ex. 10 at p. 509, col. 1.]

35. Two years later, we reported the results from the first CroFab clinical trial, demonstrating that CroFab was in fact safe and effective in a clinical setting. [Ex. 11.] CroFab was not approved until October 2000. After our 1997 article, I received many emails from clinicians asking when CroFab would be available, and I continued to receive that question whenever I attended professional meetings. Clinicians were clamoring to get CroFab. The consensus among the inquiring clinicians, which I shared, was that CroFab was so vastly superior to ACP in safety and in efficacy that it would completely supplant ACP in the market.

36. That is in fact what happened. CroFab could not be produced fast enough to meet the initial demand, and Wyeth announced that it was going to discontinue production of ACP within a year of CroFab's launch. [Ex. 12 at p. 32.] I recall Wyeth being vague about why they were discontinuing ACP, but those in the field viewed it as a recognition of what we all felt at the time; CroFab was so vastly superior to ACP that we all wanted to use CroFab if given a choice.

37. The essentially immediate substitution of CroFab for ACP is particularly striking in light of the significant cost premium for CroFab. CroFab was more expensive per vial than ACP, and treatment requires more vials than ACP due to its shorter half-life. Standard dosing for a moderate envenomation with ACP would cost a hospital $3,812.50-$6,862.60, while treatment with CroFab would cost the hospital $10,750-$19,350—almost 3 times as much. [Ex. 13 at pp. 225-226.] Despite that significant cost premium, clinicians pushed their hospitals to stock CroFab and stopped ordering ACP soon after the launch of CroFab.

38. For the above reasons, I believe that the Decision does not reflect how those of ordinary skill in the art would have viewed the claimed invention, nor does it reflect how those of ordinary skill in the art would have viewed the teachings of the prior art. The Sullivan et al. and Coulter et al. articles, and any other articles I know, would not have provided one of ordinary skill in the art with a reasonable expectation that an antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and a pharmaceutically acceptable carrier, would neutralize the lethality of the venom of a snake of the Crotalus genus.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6/8/10

Richard C. Dart, M.D., Ph.D.